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PATENT ABSTRACTS OF JAPAN

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(54) PERCUTANEOUS ABSORPTION TYPE PREPARATION

(57)Abstract:
PURPOSE: To obtain a percutaneous absorption type preparation, capable of enhancing percutaneous permeability to an anesthetic agent and manifesting a sufficient anesthetizing effect, containing a rubber type pressure sensitive adhesive and an amide type local anesthetic agent.
CONSTITUTION: An amide type local anesthetic agent (e.g. lidocaine) is contained in a base of pressure sensitive adhesive. In these circumstances, by using a rubber type pressure sensitive adhesive such as a styrene-isoprene-styrene block copolymer, as the pressure sensitive adhesive of a constituting component of the base of pressure sensitive adhesive, since the rubber type pressure sensitive adhesive extracts lipid components from a skin, the lipid components migrates into the pressure sensitive adhesive, the anesthetic agent dissolves into the migrated lipid components, percutaneous permeability to the anesthetic agent is enhanced by an increase of a dissolution rate to manifest sufficient efficacy. This preparation contains 5-80wt.% of the anesthetic agent against a total weight of the pressure sensitive adhesive and the amide type local anesthetic agent. It can remove a patient's pain caused by a therapy or a treatment on a surface of skin such as a needling, depletion of varicella or a puncture, effectively with simplicity.

LEGAL STATUS
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* NOTICES *

CLAIMS

[Claim(s)]

[Claim 1] The percutaneous absorption type tablet characterized by for the aforementioned amide type local anesthetic being the percutaneous absorption type tablet absorbed endermically, and the aforementioned pressure-sensitive binder being a rubber system pressure-sensitive binder by the pressure-sensitive adhesion basis which contains an amide type local anesthetic with a pressure-sensitive binder.

[Claim 2] The percutaneous absorption type tablet characterized by for the pressure-sensitive adhesion basis which contains an amide type local anesthetic with a pressure-sensitive binder being a percutaneous absorption type tablet currently pinched between a base material and ablation material, and the aforementioned pressure-sensitive binder being a rubber system pressure-sensitive binder.

[Claim 3] The amide type local anesthetic to the total quantity of a rubber system pressure-sensitive binder and an amide type local anesthetic is the percutaneous absorption type tablet according to claim 1 or 2 which is 30 - 60 % of the weight 15 to 70% of the weight especially preferably five to 80% of the weight comparatively.

[Claim 4] A percutaneous absorption type tablet given in any 1 term of claims 1-3 whose rubber system pressure-sensitive binder is a styrene-isoprene-styrene block copolymer.

[Claim 5] A percutaneous absorption type tablet given in any 1 term of the claims 1-4 whose amide type local anesthetic is a lidocaine or its hydrochloride.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] this invention relates to the percutaneous absorption type tablet which contains the amide type local anesthetic represented by a lidocaine or its hydrochloride as an active principle.
[0002]
[Description of the Prior Art] The external application tablet for applying to the skin or the mucosa containing an amide type local anesthetic like a lidocaine is considered variously conventionally, and the ointment or the liquefied tablet of that is used by clinical.
[0003] Although the tablet of such a gestalt is used mainly for the topical anesthesia, it is not suitable removing an ache to satisfaction in the case of disposal, like it is difficult for the skin permeability of an amide type local anesthetic to obtain sufficient effect of a medicine for a low reason, therefore it removes pricking and varicella in a skin front face. Especially, since a child holds an exceptional feeling of fear to this kind of ache and treatment is often barred, development of the tablet which can fully remove such an ache is desired. Moreover, although the ache produced in the case of a puncture is the problem which cannot be disregarded on clinical regardless of age or sex, the above conventional tablets cannot fully remove such an ache. Furthermore, these ointments' or liquefied tablets' having un-arranged [of soiling a finger and a hand in the case of medication, or soiling clothes etc. after medication], and cannot be called what offers a simple medication method.
[0004] moreover, the macromolecule system polymer which is a pressure-sensitive adhesive property in ordinary temperature in JP,60-185713,A -- receiving -- the concentration more than saturation solubility -- a percutaneous absorption medicine -- **** -- the recrystallization particle state of a uniform size -- this polymerization -- the percutaneous absorption tablet with the adhesive layer currently distributed inside of the body is proposed however -- since, as for the thermodynamic activity of a percutaneous absorption medicine, the concentration of that in a basis serves as the maximum by the saturation state, although skin permeability increases with elevation of the medicine concentration in a basis to a saturation state -- a macromolecule system polymerization -- even if it raised the concentration of the percutaneous absorption medicine contained inside of the body more than the saturation solubility of that, it was expected as that to which the skin permeability of a percutaneous absorption medicine does not go up more than the skin permeability shown according to a saturation state Moreover, the problem that the small dissolution rate of that will serve as an obstacle if the crystal of a medicine is hard, and percutaneous absorption became late as a result was expected.
[0005]
[Problem(s) to be Solved by the Invention] Therefore, the amide type local anesthetic was supplied in the skin with high skin permeability, and an appearance of the percutaneous absorption type tablet which can demonstrate sufficient anesthesia effect by it was desired.
[0006]
[Means for Solving the Problem] When this invention person makes an amide type local anesthetic contain in a pressure-sensitive adhesion basis as a result of repeating research variously in view of an above-mentioned situation and it considers as a percutaneous

absorption type tablet If the pressure-sensitive binder which is the constituent of this pressure-sensitive adhesion basis is made into a rubber system pressure-sensitive binder like a styrene-isoprene-styrene block copolymer, in order that this rubber system pressure-sensitive binder may extract a lipid component from the skin This lipid component shifted into the above-mentioned pressure-sensitive adhesion basis, and it found out that the skin permeability of an anesthetic increases as a result of the above-mentioned anesthetic's dissolving into this lipid component that shifted and the dissolution rate of that going up, and the effect of a medicine high enough was obtained promptly.

[0007] this invention was invented based on the above-mentioned knowledge, and makes the high skin permeability of an amide type local anesthetic attain. It aims at offering the percutaneous absorption type tablet which can demonstrate the effect of a medicine high enough. The percutaneous absorption type tablet characterized by for the aforementioned amide type local anesthetic being the percutaneous absorption type tablet absorbed endermically, and the aforementioned pressure-sensitive binder being a rubber system pressure-sensitive binder by the pressure-sensitive adhesion basis which contains an amide type local anesthetic with a pressure-sensitive binder is started.

[0008] The lipid component which exists in a skin front face with a rubber system pressure-sensitive binder in this invention, Cholesterol or a ceramide can be extracted efficiently. For example, the result, What can raise promptly the solubility of the amide type local anesthetic to a basis is said. For example, a styrene-isoprene-styrene block copolymer, natural rubber, The basis containing this rubber system pressure-sensitive binder and an amide type local anesthetic silicone rubber etc. by consisting of a styrene-isoprene-styrene block copolymer especially preferably By the case, a tackifier, for example, rosin, a terpene, a synthetic-petroleum resin, Phenol resin etc.;; bulking agents, such as a softener, for example, a liquid paraffin etc. For example, titanium oxide, a calcium carbonate, a magnesium carbonate, calcium, Antioxidants, for example, a dibutyl hydroxy toluene, such as a magnesium carbonate, a silicate, and an aluminum hydrate, and/or burylhydroxyanisole, a styrene-ized phenol, zinc dibutyldithiocarbamate, etc. can be included.

[0009] As an amide type local anesthetic used in this invention, a lidocaine, a dibucaine, the bupivacaine, prilocaine, MEPIBAKAIN, those hydrochlorides, or an oxethazaine is mentioned, for example. In this, comparatively, since soluble improvement according [the melting point] to a skin lipid a low sake is easy to be attained, a lidocaine and prilocaine are the anesthetics suitable for especially using by this invention.

[0010] Generally the rate of the amide type local anesthetic to the total quantity of a rubber system pressure-sensitive binder and an amide type local anesthetic is 30 - 60 % of the weight about 15 to 70% of the weight especially preferably about five to 80% of the weight.

[0011] As for the percutaneous absorption type tablet by this invention, it is desirable that it is in the form of a tape. this invention tablet of the form of a tape is a tablet characterized by for the pressure-sensitive adhesion basis which contains an amide type local anesthetic for example, with a pressure-sensitive binder being a percutaneous absorption type tablet currently pinched between a base material and ablation material, and the aforementioned pressure-sensitive binder being a rubber system pressure-sensitive binder.

[0012] The film or sheet which can use any base material if it is the base material usually used in the common tape as a base material, for example, consists of a polyethylene terephthalate, polyethylene, polypropylene, a polyvinyl chloride, a polycarbonate, polyurethane, a polyimide, a polytetrafluoroethylene, or a polyvinylidene fluoride is mentioned. The thickness of these films or a sheet is about 10-100 micrometers preferably. When injecting through this tape, the tape which has the small base material of resistance to a hypodermic needle is desirable.

[0013] What coated a film or a sheet which could use any ablation material when it was the ablation material usually used in the common tape as ablation material, for example, was mentioned above as paper or a base material with the remover which has ablation functions, such as silicone, is mentioned.

[0014] The percutaneous absorption type tablet by this invention for example, a solvent like ethyl acetate In order to consider as a tape after stirring until it mixes with an amide type local

anesthetic and a rubber system pressure-sensitive binder and becomes homogeneous about this mixture for example After extending on a base material in the form of a stratified basis where the obtained homogeneous mixture is dropped on a base material, and it has fixed thickness, this is dried and a solvent is removed, and subsequently to between a base material and ablation material, it is manufactured by covering a basis by ablation material so that a basis may be pinched.

[0015]

[Example] Hereafter, although this invention is explained based on an example, this invention is not limited to these examples.

[0016] 1g in all and 2g of ethyl acetate were mixed, the lidocaine of the rate shown in example 1 table 1 and the styrene-isoprene-styrene block copolymer were stirred until it became homogeneous, the optimum dose in the obtained mixture was dropped on the polyethylene-terephthalate film with a thickness of 50 micrometers, this was quickly extended with a thickness of 50-60 micrometers in the shape of a film on the film using the applicator, and it dried at 40 degrees C. Tapes 1-7 were obtained after dryness by sticking the polyethylene-terephthalate film with which silicone is coated to a basis.

[0017]

表1 (単位：重量%)

	テープ剤						
	1	2	3	4	5	6	7
リドカイン	0	10	20	30	40	50	60
スチレン-イソプレン-スチレンブロック共重合体	100	90	80	70	60	50	40
リドカイン濃度（重量%）	0	10	20	30	40	50	60

The saturated concentration of the lidocaine in the pressure-sensitive adhesion basis which contains a lidocaine with a styrene-isoprene-styrene block copolymer is 20 % of the weight, and the lidocaine which remains with a crystallized state in addition to the lidocaine which has melted to this saturated concentration in tapes 4-7 also lives together.

[0018] The abdomen extraction skin of an example 2 male hair loess rat (7-8 weeks old) is applied to 2-chamber diffusion cell which circulated 37-degree C water. The tapes 1-7 (thing except ablation material) with a diameter of 10mm pierced circularly were beforehand stuck on the horny layer side of the skin (with the amount:tapes 1-7 of the lidocaine applied to the horny layer side of the skin). respectively -- 0microg, 500microg, 1000microg, 1500microg, 2000microg, 2500microg, and 3000microg Water was applied to the dermis side of the skin. The amount of the lidocaine which extracted with time the water applied to the dermis side, and penetrated the skin using the high performance chromatography was measured. Moreover, the amount of accumulation of the lidocaine which penetrated the skin is shown in drawing 1 .

[0019] Furthermore, the skin transmission rate of a lidocaine was calculated from these values. The result is shown in drawing 2 . Xylocaine jelly (product made from FUJISAWA pharmaceutical industry, 2 % of the weight of lidocaine-hydrochloride content) 0.03g currently used by the present clinical one was applied to the horny layer side of the skin for comparison (amount:500microg of the lidocaine applied to the horny layer side of the skin (converting into a lidocaine)). Then, as it mentioned above, the amount of the lidocaine which penetrated the skin was measured, and the amount of accumulation transparency of the lidocaine obtained as a result was shown in drawing 1 .

[0020] In the tape by this invention, these results show that a skin transmission rate also goes up with elevation of the concentration, when concentration (content in a basis) of a lidocaine is made higher than saturated concentration (20 % of the weight).

[0021] Moreover, it turns out that the tape by this invention shows the high amount of accumulation transparency compared with the xylocaine jelly currently used by the present

clinical one.
The influence of the skin lipid component exerted on an example 3 this-invention tape was investigated. With the application of [for 5 hours] the tape 1 which does not contain the lidocaine manufactured in the example 1, the skin lipid component was extracted at the abdomen of a hair loess rat. Then, the bases of the tape 1 with which the skin lipid component is extracted, and the tape 6 with which a part of lidocaine exists by the crystallized state, and it contains 50% of the weight of a lidocaine on the whole were stuck mutually, this was left at 37 degrees C for 48 hours, and the lidocaine in a tape 6 was dissolved into the tape 1 by it (diffusion). The heat of fusion of the lidocaine crystal in a tape 1 and 6 was measured using DSC (differential scanning calorimeter), and the decrement of a crystal was computed (this invention experiments 1-3). For comparison, the total quantity of the lidocaine crystal in a tape 1 and 6 was similarly computed using the unsettled tape 1 (comparative experiments 1-3). These results are shown in Table 2.
[0022]
[Table 1]
表2：本発明による鉄剤に及ぼす皮膚脂質成分の影響

	テープ剤1密着前のテープ剤6			テープ剤1と密着したテープ剤6			リドカイン結晶の減少率 (%)	平均 (%)	S.E. (%)
	重量(g)	cal/g	リドカイン結晶の量 ($\times10^{-3}$, g)	合計重量(g)	cal/g	リドカイン結晶の量 ($\times10^{-3}$, g)			
本発明実験1	0.0601	-2.340	5.3881	0.0809	-1.195	3.7039	31.26		
本発明実験2	0.0596	-2.340	5.3432	0.0804	-1.009	3.1081	41.83	35.61	1.45
本発明実験3	0.0602	-2.340	5.3970	0.0806	-1.158	3.5759	33.74		
比較実験1	0.0615	-2.340	5.5136	0.0782	-1.643	4.9225	10.72		
比較実験2	0.0619	-2.340	5.5494	0.0793	-1.657	5.0647	8.78	11.40	2.61
比較実験3	0.0572	-2.340	5.1281	0.0710	-1.607	4.3714	14.26		

[0023] The result shown in Table 2 shows that the solubility of the lidocaine in a basis is increasing when the skin lipid component was extracted by the basis.
[0024]
[Effect of the Invention] As a result of the solubility of an amide type local anesthetic increasing in a basis according to this invention so that clearly from the explanation described above, the dissolution rate of that goes up. Since the percutaneous absorption type tablet which can supply the high-concentration anesthetic which the skin permeability of an anesthetic improves and demonstrates sufficient effect of a medicine promptly by it to a part for the skin and the periphery is offered A patient's ache produced by the treatment or disposal of pricking in a skin front face, varicella removal, or a puncture can be removed effectively and simple, therefore the effect of becoming easy to carry out such treatment or disposal is acquired.

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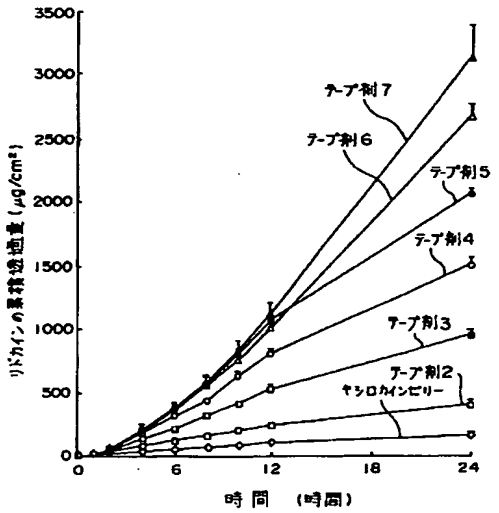
DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]
[Drawing 1] It is the graph which shows the amount of accumulation transparency of the lidocaine about the tapes 1-7 measured in the example 2.
[Drawing 2] It is the graph which shows the skin transmission rate of the lidocaine called for in the example 2.

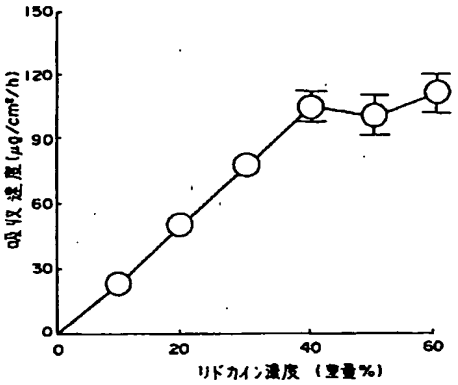
[Translation done.]

Drawing selection drawing 1



[Translation done.]

Drawing selection drawing 2



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